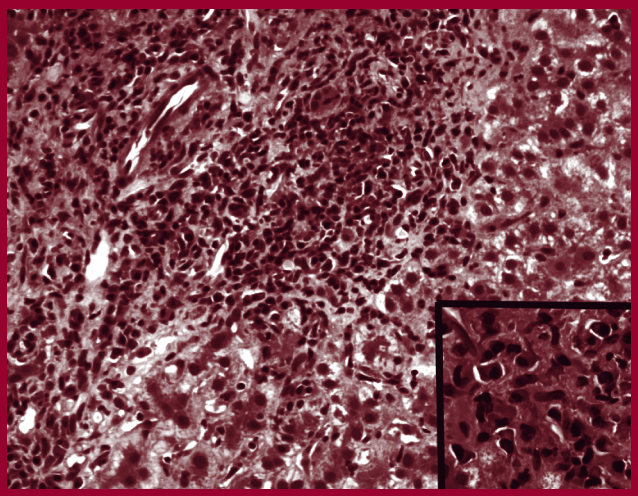
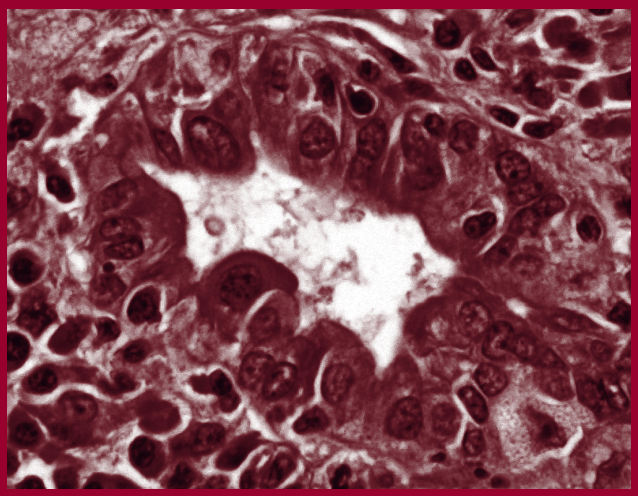
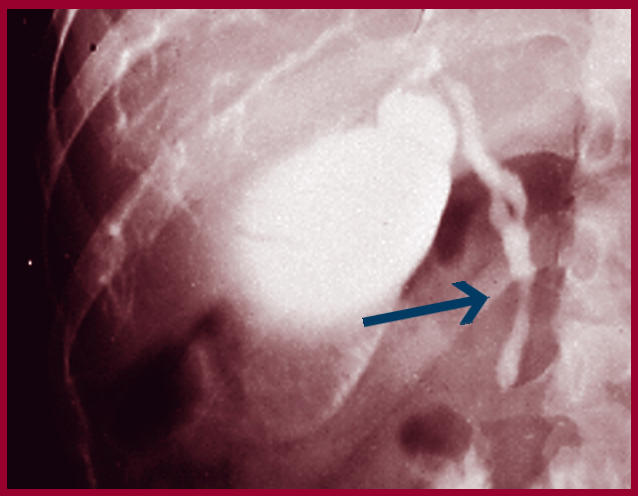


Autoimmune Hepatitis



Primary Biliary Cirrhosis



Primary Sclerosing Cholangitis

Autoimmune liver disease occurs when the body reacts inappropriately to its own cellular components and includes autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis.

TOP: A liver biopsy from a patient with autoimmune hepatitis shows infiltration of immune cells such as plasma cells (see inset for closer view of plasma cells). Photo: Dr. Zachary Goodman, Division of Hepatic Pathology, Armed Forces Institute of Pathology.

MIDDLE: A liver biopsy from a patient with primary biliary cirrhosis shows a bile duct lesion. Photo: Dr. Zachary Goodman, Division of Hepatic Pathology, Armed Forces Institute of Pathology.

BOTTOM: An endoscopic retrograde cholangiopancreatograph (ERCP) from a patient with primary sclerosing cholangitis shows strictures in the extrahepatic bile ducts (arrow). Photo: Dr. Sandy Irani, George Washington University.

CHAPTER 9:
AUTOIMMUNE LIVER DISEASE

INTRODUCTION AND BACKGROUND

Autoimmune liver diseases include autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. All three diseases can be severe, progressive, and lead to cirrhosis and death from end-stage liver disease. Because none of the currently available therapies are curative, these diseases remain important causes of liver failure requiring transplantation. Strikingly, these diseases recur in 10 to 30 percent of patients after liver transplantation.

Autoimmune hepatitis affects approximately 17 persons per 100,000 population. Autoimmune hepatitis occurs most commonly in women, particularly during adolescence, but this disease can occur at any age, in both men and women, and in persons of any race or ethnicity. Autoimmune hepatitis often results in severe hepatitis that can rapidly progress to cirrhosis. Diagnosis is based upon clinical features, the presence of autoantibodies, histology, and the absence of other causes such as viral hepatitis. Standard immunosuppressive therapy using corticosteroids with or without azathioprine is effective in decreasing mortality, but progression to cirrhosis while on therapy may occur. In most cases, therapy must be continued lifelong, and numerous side effects of therapy are common. If therapy is delayed or ineffective, liver transplantation may be required. Currently, 3 percent of adult liver transplants performed in the United States are for autoimmune hepatitis.

Primary biliary cirrhosis or "PBC" is a progressive cholestatic liver disease that affects approximately 40 adults per 100,000 population. The diagnosis is usually made in middle age, and women outnumber men by a ratio of 10:1. The disease is characterized by inflammation and gradual destruction of small intrahepatic bile ducts. Diagnosis is based upon biochemical tests, compatible liver histology, and the presence of antimitochondrial antibodies (AMA) or disease-specific antinuclear antibodies. PBC slowly, but almost invariably, progresses to cirrhosis over 10 to 30 years, and the diagnosis is often made late in its natural history. The hydrophilic bile acid ursodiol is effective in decreasing liver injury due to cholestasis and in retarding the progression of disease. Patients who develop decompensated cirrhosis require liver transplantation. Presently, 4 percent of liver transplants in the United States are done for PBC.

Primary sclerosing cholangitis or "PSC" is also a progressive cholestatic liver disease that affects approximately 8.5 persons per 100,000 population. It occurs in children and young adults and is more common in men than women. A majority of patients have associated inflammatory bowel disease, primarily ulcerative colitis. PSC is marked by inflammation and destruction of the intra- and extra-hepatic bile ducts (larger than those affected by PBC). The diagnosis is made based upon typical clinical presentation, biochemical tests, compatible liver histology, and strictures of bile ducts as detected by endoscopic retrograde cholangiopancreatography (ERCP) or imaging.

PSC is a progressive disease, which leads to gradual sclerosis of major bile ducts with resulting cholestasis, fibrosis and cirrhosis. Patients with PSC are at high risk of cholangiocarcinoma regardless of the stage of disease. Those with ulcerative colitis also have an increased risk of colon cancer. There are no proven curative therapies for PSC, but high doses of ursodiol may retard progression. At present, 6 percent of adult liver transplants in the United States are done for PSC.

RECENT RESEARCH ADVANCES

Advances in research on autoimmune liver disease have occurred in understanding its pathogenesis and improving its management.

Understanding Autoimmmunity: A major focus of research has been on the nature of autoimmunity itself. The causes that trigger autoimmunity (afferent limb) are unknown, and the pathogenesis of injury (efferent limb) is only poorly defined. At issue is why patients develop an aberrant immune response to a self-antigen and how this breakdown of tolerance leads to clinical disease. Theories for the basis of autoimmunity include genetic predisposition, inherited abnormalities of immune regulation, molecular mimicry between an environmental or infectious agent and an autoantigen, and occult infectious disease that triggers an autoimmune process. Recent clues to the etiology of autoimmunity come from studies of inherited diseases of immune regulation in which dysregulation of T cell proliferation is associated with multiple autoimmune conditions. These studies point to immune regulation as central to the etiology of autoimmune diseases.

Understanding Causes of Autoimmune Liver Diseases: Ongoing research in autoimmune liver diseases has focused on identifying autoantigens and the association of immune responses (largely CD4+ and CD8+ T cell responses) to these antigens with disease manifestations. Autoimmune hepatitis has a strong genetic component and has been linked to an extended HLA haplotype (A1-B8-DR3). The autoantigens of classical (type I) autoimmune hepatitis are directed toward multiple nuclear antigens, while those in a subgroup of disease (type II) have been shown to be specific for the hepatic drug metabolizing enzyme, CYP 2D6. PSC also exhibits strong genetic susceptibility linked to three HLA class II haplotypes. The autoantigens in PSC have not been defined, although many patients have antibodies to neutrophil nuclear antigens that are similar to perinuclear neutrophil cytoplasmic antibodies present in ulcerative colitis. PBC has only weak HLA associations. The autoantigen of PBC, however, has been well characterized, the typical antimitochondrial antibodies being directed toward the E2 component of the mitochondrial pyruvate dehydrogenase complex. Both B and T cell responses to the E2 autoantigens have been defined, but the genetic or environmental causes that drive these immune responses remain unclear. Interestingly, human AMA cross-reacts with both chemical and bacterial antigens, some of which are broadly present in the environment.

Developing Therapies for Autoimmune Liver Diseases: Attempts to develop animal models of autoimmune liver disease have been only partially successful. As a consequence, advances in therapy of autoimmune liver diseases have relied on human studies. Studies from the late 1960s and early 1970s helped define the current regimen of therapy of autoimmune hepatitis, which is the combination of corticosteroids and azathioprine. There has been little improvement on therapy since then, despite the recent development of a broad armamentarium of immunosuppressive medications. The current therapy for PBC is the long-term use of ursodiol, a safe and well tolerated hydrophilic bile acid, which appears to act by replacing naturally produced hydrophobic and hepatotoxic

bile acids. Combined analyses of four large multicenter trials of ursodiol have shown that therapy improves survival, but does not result in reversal or cure of disease. Clearly, therapy of PBC warrants further investigation, particularly with the availability of more potent and specific immune-modulatory and anti-inflammatory agents. Finally, current therapy for PSC is problematic and unsatisfactory. Large-scale trials of high-dose ursodiol therapy are currently under way, but there is little evidence that ursodiol has any action beyond slowing the progression of disease. Thus, therapies for autoimmune liver disease are limited to medications that blunt the effector or efferent limb of the response. None are directed at the still elusive fundamental causes of these diseases.

RESEARCH GOALS

The major goals for research in autoimmune liver diseases are to understand the etiology and pathogenesis of these three diseases and to develop effective means of treatment and prevention.

Basic Research on Pathogenesis: Progress in research on autoimmune liver disease is hampered by the lack of accurate animal models of these diseases. Current mouse models such as the concanavalin A-treated or Met-Kb transgenic mice focus on a narrow component of immune hepatic injury and do not reflect the complexities of the human diseases. Most mouse models reflect acute hepatocellular injury only, and rely upon one or a few pathways of cell injury or destruction. Fully realized models should reflect the chronic nature of these disorders and exhibit chronic necroinflammation and fibrosis.

- *Research Goal:* To develop animal models for each of the autoimmune liver diseases (Matrix Cell B3; see also Chapter 15, A2).

In other disciplines, such as diabetes, rheumatology, and gastroenterology, murine models of human diseases have been helpful in elucidating pathogenesis (e.g., insulitis in type 1 diabetes), as well as providing insights into targets for therapy (e.g., anti-TNF for rheumatoid arthritis and Crohn's disease). Several pathways might be taken to develop animal models of autoimmune liver diseases. These might include:

- Mouse mutagenesis studies combined with a practical screen for both liver disease and autoimmunity (such as serum ALT levels and T cell activation markers);

- Innovative means of expressing neoantigens in liver and bile ducts in adult animals while avoiding thymic tolerance (e.g., by conditional liver-specific expression of transgenes);

- Ablation of normal mechanisms of hepatic immune tolerance (e.g., by increasing pro-inflammatory or decreasing anti-inflammatory cytokine expression in liver in transgenic animals); or

- Development of models of non-specific, bystander injury to the liver (e.g., by the homing of cytotoxic T cells to the liver and the disposition of these T cells during extrahepatic viral infection).

The effort to develop animal models for autoimmune liver diseases would be helped by interactions with other disciplines with experience in this area.

- *Research Goal:* To convene an international, interdisciplinary research workshop on the development of animal models of autoimmune liver diseases (Matrix Cell A1).

Once murine models of disease are developed, they can provide means of defining the mechanisms of immune injury to the liver and might well provide clues to pathogenesis and insights into targets for therapy.

- *Research Goals:* To utilize animal models of autoimmune liver diseases to define the roles of the innate and acquired immune systems in these diseases and identify environmental and/or genetic triggers for induction of autoimmune hepatitis (Matrix Cells A3 and C3).

Clinical Studies of Pathogenesis, Etiology, and Therapy: Another major roadblock to progress in research on autoimmune liver diseases is that these diseases are relatively uncommon. New cases of autoimmune hepatitis, PBC, and PSC are rare, and, therefore, the numbers of patients available to be studied at the onset of disease and before treatment with immunosuppressive or other medications are few. For these reasons, patient-based research on autoimmune liver diseases would be greatly facilitated by a multicenter, nationwide network of clinical centers interested in these conditions.

- *Research Goal:* To develop multicenter clinical research networks of investigators to study the natural history, clinical course, pathogenesis, etiology, and therapy of autoimmune hepatitis, PBC, and PSC (Matrix Cell A2).

Well characterized cohorts of patients followed in a standardized fashion both in a cross-sectional manner (retrospective protocol) and from the disease onset forward (prospective protocol) would facilitate studies on the etiology of these diseases and the pathogenesis of injury.

- *Research Goal:* These studies might include:
  1. Clinical and epidemiological studies assessing risk factors and possible triggering events and comparing these diseases in different age- and racial/ethnic-groups for clues to etiology (Matrix Cell C3);
  2. Development of standardized diagnostic criteria and definitions of endpoints of successful therapy in the autoimmune liver diseases (Matrix Cell B2; see also Chapter 8, A1; Chapter 10, A1; Chapter 14, B1; and Chapter 16, A1);
  3. Proteomic analyses for serum biomarkers of disease activity and stage (Matrix Cell B2);
  4. Screens for antibodies, including use of protein arrays, at different stages of disease;
  5. Correlations of T cell responses to autoantigens to disease activity measured during flares of illness and during quiescence (Matrix Cell A3);
  6. Search for viral pathogens in liver and biliary tissue to discover therapeutic targets closer to the root causes of the diseases;
  7. Analyses of genetic linkages including use of family and sibling studies (Matrix Cell B3);
  8. Initiation of pilot studies of new approaches to therapy and development of planning groups to launch full-scale, randomized controlled trials of therapy (Matrix Cell C1); and
  9. Finally, the network could interact with currently conducted trials in PBC and PSC to facilitate ancillary studies of diagnosis, screening, pathogenesis and therapy in areas such as the role of high-dose ursodiol therapy in PSC, alternatives to standard therapy of autoimmune hepatitis, and screening tests for development of cholangiocarcinoma in PSC (Matrix Cells B1, C2, and C3; see also Chapter 15, C2).

STEPS TO ACHIEVE RESEARCH GOALS

A research workshop on animal models for autoimmune liver disease would be both practical and useful in promoting progress in studies of the pathogenesis of autoimmune liver diseases. This workshop should include discussion of animal models of other autoimmune diseases, as well as models for viral-induced liver disease. Investigator-initiated research project grants focusing on the development of animal models should be encouraged as an area of high priority. A single or several interlocking clinical research net-

works on autoimmune liver diseases would provide a strong stimulus to both clinical and laboratory research on these conditions. The network would ensure nationwide and broad representation of these diseases including patients in all age, socioeconomic, racial, and ethnic groups, reflecting the diversity of the U.S. population. The network could serve to develop practical but reliable diagnostic criteria and uniform definitions of endpoints for successful therapy. The network might interact with other NIH-funded networks (e.g., inflammatory bowel disease or type 1 diabetes networks) with joint or collaborative projects. The network could also serve to help investigators share resources and apply newer techniques to issues in autoimmune liver diseases. Examples of new techniques that might be investigated or facilitated by a clinical research network include imaging modalities aimed at *in vivo* identification of inflammation and neoplasia in bile ducts; molecular fine-definition of B and T cell reactivities present in liver biopsy tissue; application of proteomics, gene expression arrays, and haplotyping to serum, DNA, and tissue samples acquired by the network; and direct translation of findings from animal model research to human disease.

Matrix of Research Goals in Autoimmune Liver Disease

	Short Term (0-3 years)	Intermediate Term (4-6 years)	Long Term (7-10 years)
High Risk	**A3.** Define the roles of CD4+ and CD8+ T cells, other effector immunocytes, dendritic cells, and the innate immune system in liver injury in humans (and animal models) with autoimmune liver disease.	**B3.** Identify genetic linkages in PBC and refine the HLA-associations in autoimmune hepatitis and PSC. Develop animal models for each of the autoimmune liver diseases.	**C3.** Identify modifiable environmental (with or without genetic) triggers for induction of autoimmune hepatitis (from human studies or murine models).
Intermediate Risk	**A2.** Develop multicenter networks of investigators to study natural history, pathogenesis, etiology, and therapy of autoimmune liver diseases.	**B2.** Develop sensitive and specific biomarkers for disease activity and stage in PBC and PSC. Develop diagnostic criteria and standard definitions for endpoints of therapy.	**C2.** Develop sensitive serum markers for early detection of cholangiocarcinoma in PSC.
Low Risk	**A1.** Organize and convene an international, interdisciplinary research workshop on development of animal models of autoimmune liver diseases.	**B1.** Demonstrate whether high-dose ursodiol therapy is effective in retarding the progression of PSC and identify risk factors for progression and for response to treatment.	**C1.** Develop alternatives to prednisone/azathioprine as maintenance therapy of autoimmune hepatitis and define markers for when and how therapy can be safely stopped.